The Collagen Diseases

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SUMMARY

The collagen diseases have in common certain relatively specific alterations in the tissues that are derived from the mesenchyme.

In reviewing the development of this concept, the nature and the pathogenesis of these changes and the blocking effect of cortisone and ACTH are discussed.

The term "diseases of the collagen system" includes a number of clinical states within a broad spectrum of variation in the basic alterations of collagenous and vascular tissues. In rheumatoid arthritis the modifications are chiefly in the somatic connective tissue; in periarteritis nodosa the blood vessel involvement is preeminent; dermatomyositis and disseminated lupus erythematosus present more intermediate mixtures of these changes.

THE principal site of the morphologic changes of the collagen diseases is in the connective tissues widespread throughout the body. The cells of this tissue, derived from primitive fibroblasts, have long had a recognized position in the understanding of certain pathologic processes, such as repair. The intercellular substance is made up of fibers embedded in a homogeneous matrix, or ground substance. The structural and mechanical functions of connective tissue are performed particularly by its collagenous, elastic, and reticulum fibers. This fiber component justifies the name of the tissue, for it connects other structures; serves as the framework for the parenchymatous cells; and, frequently, as in the heart valves, provides essential working parts of organs. The ground substance, homogeneous and colloidal in nature, is concerned with the less obvious functions of connective tissue in the transfer of metabolites, and in electrolyte and water balance. As the term "collagen" is the Greek for "glue-forming," it is appropriate as a synonym to designate this tissue. (In a fundamental experiment an animal glue is obtained by the boiling of connective tissue.) Such a chemical term more intimately connotes the metabolic activities of the tissue and its features of permeability.

In its derivation from mesenchyme, collagenous tissue has a close ontogenetic association with reticulum and the reticuloendothelial system, mesothelium and endothelium, smooth muscle, and the dense structural tissues. Aegerter and Long[1] recently emphasized that basic defense activities are shared by these mesenchymal derivatives. Hence, it is understandable that the pathological alterations of the collagen system are intimately related to morphologic changes in the ubiquitous branches of the vascular system and in the serous membranes, and to the chemical activities mediated by the reticuloendothelial system.

Histopathologic alterations peculiar to the intercellular portion of connective tissue were observed as long ago as 1880 by Neumann. The term "fibrinoid degeneration" was applied to an acellular, refractile, homogeneous material change that had the prominent eosinophilic staining reaction of fibrin. In undergoing fibrinoid degeneration, the collagen fibers were noted to be swollen and fragmented and the ground substance increased in amount, acquiring an unusual density and striation. Subsequent observers described this change in various inflammatory and degenerative states. Klinge,[19] in 1933, considered it of primary importance in the tissue modifications of rheumatic fever. Studies of the microscopic features of such diseases as disseminated lupus erythematosus and scleroderma gradually developed the recognition of a basic pattern of diffuse vascular and collagen system alteration.[3]

In 1941, Klemperer and his associates[18] summarized their observations on the widespread fibrinoid formation and swelling of the ground substance of the collagenous tissue in the heart, blood vessels, serous membranes, joint capsules, dispersed connective tissue and skin, as well as the characteristic splenic and renal lesions, in disseminated lupus erythematosus. They expressed the concept of the basic importance of such morphologic alterations of the collagen system, establishing the terms "collagen disease" and "diseases of the collagen system."

Fibrinoid degeneration, vascular necrosis, and fibrosis have been encountered as a common denominator in the histopathologic changes of serum sickness, periarteritis nodosa, disseminated lupus erythematosus, rheumatic fever, rheumatoid arthritis, scleroderma, and dermatomyositis. These diseases are recognized as members of the collagen disease group, representing a spectrum of similar alterations in collagenous tissue in dissimilar degrees and distribution. Unrestricted interpretation of fibrinoid vascular change has led various proponents to include in this group such diseases as glomerulonephritis, malignant hypertension, thromboangiitis obliterans, and the Schönlein-Henoch syndrome.[6] But there has not been general acceptance of such inclusions. Against the natural tendency to give a totally common identity to the collagenous diseases, Klemperer[17] has steadfastly maintained that each disease is a separate entity with its own specific anatomical and clinical definition, even though the changes it causes occur in a common systemic site.

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Yardumian and Kleinerman[33] presumed that the blood vessel lesion is antecedent to fibrinoid degeneration, and proposed the term "panarteriolitis" to describe the varied alterations of degenerative, proliferative, and inflammatory nature found in the blood vessels. They interpreted the vascular and collagenous changes in these diseases as representing an "accelerated aging" of these tissues, rather than as a unique process.

The role of allergic reaction as an etiologic factor was originally suggested by clinical considerations and supported by the studies of the German pathologists[8, 20] from 1923 to 1938. Rich,[25] since his observations in 1942 on periarteritis nodosa, serum sickness, and sulfonamide therapy, has ably championed the view that fibrinoid collagenous change and the associated arteriolar reaction are manifestations of hypersensitivity. These alterations have been produced experimentally on a hypersensitivity basis by Rich and Gregory[26] and by subsequent workers up to the present. Similar changes are repeatedly observed in microscopic examination of tissues from subjects with allergic conditions. The author observed pronounced fresh fibrinoid necrosis of arterioles widespread in the various organs in a year-old child who died in an acute state of allergic disease. The increase in eosinophilic leukocytes in the blood which has been observed in association with a number of the collagen diseases lends further support to the belief in allergic sensitivity as a causative factor.

As similar collagen changes can be produced by factors apparently unrelated to hypersensitivity, the specificity of fibrinoid degeneration becomes a paramount question. As originally defined and subsequently interpreted, fibrinoid material is characterized by the morphologic phase of homogeneity with refractility and eosinophilic staining reaction. Its appearance suggests a modification of the colloidal state similar to that of coagulation necrosis. Fibrinoid material has been observed in association with many bacterial infections, in the bed of peptic ulcers, and in the vessels of subjects with experimentally induced hypertension; and it has been produced by simple squeezing of the skin. It cannot be assumed to be a specific or pathognomonic manifestation of the hypersensitive state as that state is ordinarily understood.

Significant advances have been made in elucidating the physical and chemical nature of collagen, and therein lies the hope of ultimately understanding its pathological alterations. The electron microscope has revealed essential differences in its nodal structure.[7] The ground substance is a gel composed of acid mucopolysaccharides like hyaluronic acid. Such compounds are highly viscous, and their state of phase and water content are sensitive to pH change due to their high polymerization. Hyaluronidase reduces their viscosity. It appears that fibrinoid material is formed by precipitation of the acid mucopolysaccharides of the ground substance, and that the precipitation possibly is caused by an alkaline protein derived either from necrotic tissue or from reaction with a damaging reagent. Fibrinoid material can be identified by its positive reaction with the Schiff reagent after periodic acid oxidation.[2]

The formation of plasma globulin, especially the immune globulins of the gamma type, is attributed to the reticuloendothelium. If collagenous alterations are interpreted as a part of a defense reaction of the mesenchyme in which reticulum participates, there is a logical correlation with the hyperglobulinemia frequently encountered in collagen diseases. In explaining the emphasized reaction of the connective tissue cells, Aegerter and Long[1] postulated the formation of antibodies which are retained in the cytoplasm of the cellular elements and which participate in an intracellular hypersensitivity reaction. This appears to be substantiated by the work of Warren and Dixon[32] in which radioactively labeled antigen was located in the edematous peribronchial tissues in experimentally induced anaphylactic shock.

Changes in the collagenous subcutaneous tissue in various endocrine states, such as hypothyroidism, have long been recognized. Selye[27] demonstrated experimentally the production of mucinous edema by estradiol. An extension of the same investigator's concept of adaptation exposes the role of cortical adrenal activity in the body defense reaction.[28] In 1948, it was found that ACTH caused a drop in the gamma globulin.[4] The epochal work of Hench, Kendall, and co-workers[12] has shown the astounding temporary efficacy of ACTH and cortisone (Kendall compound E) in rheumatoid arthritis, rheumatic fever, and other members of the collagen disease group. Any excitant of adrenal cortical activity, such as epinephrine or insulin, appears to have a similar although lesser effect. Both ACTH and cortisone regularly depress the gamma globulins,[13] reduce the eosinophilic leukocytes of the blood,[31] and inhibit the proliferation of fibroblasts. The healing of wounds[23] and fractures[24] is powerfully inhibited by these substances. Adrenal steroids have an inhibitory effect on the "spreading factor" of the skin. The hyperadrenal state induced directly by cortisone, or indirectly by ACTH, appears to block the usual mesenchymal tissue reactions, whether expressed as wound healing or the development of hypersensitivity. Perhaps this is accomplished in part by alterations in tissue permeability.[5] The voluminous work being published currently on the activity of ACTH continually exposes new, beneficial effects of ACTH in the collagen diseases[22] and constitutes one of the most brilliant chapters of American medicine.

In explaining the individual differences in the separate diseases which are associated as the collagen group, it has been proposed that these differences are accounted for by the variations in the provocative antigenic agents, the hormone control, and the constitutional predisposition which affects the mesenchymal defense unit.[1] The multitude of similarities and the specific differences of the collagenous diseases have been summarized in the recent publications of Stewart[30] and Kampmeier.[14]

Procedures identifying the individual diseases are becoming more numerous. Periarteritis nodosa is being diagnosed frequently by biopsy.[16] In active rheumatoid arthritis, intramuscular aggregates composed of a central nodule of lymphocytes surrounded by plasma cells have been observed regularly.[21, 29] A particular cell, the "L.E." cell, has been found in the blood and bone marrow in disseminated lupus erythematosus.[10] This cell is an expanded polynuclear leukocyte containing vacuoles of nuclear chromatin in various stages of digestion. That the agent responsible for this lytic-phagocytic phenomenon resides in the globulin of the blood is demonstrated by the regular appearance of "L.E." cells in large numbers in normal bone marrow to which serum from a person who has disseminated lupus erythematosus is added.[11]

These recent advances appear to support and expand the basic concept that a similar pathologic process of mesenchymal tissue finds expression in the various collagen diseases. As a basic tissue reaction mechanism, it holds a position analogous to that of suppurative inflammation. Throughout the varied etiologic features of the individual diseases, there is the recurring suggestion of hypersensitivity, and modification by constitutional and endocrinous factors. The control exerted upon mesenchymal tissue reaction, either indirectly by ACTH, or directly by cortisone, aids in the understanding of the functional activity of the tissue and opens new vistas of therapeutic possibilities.

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